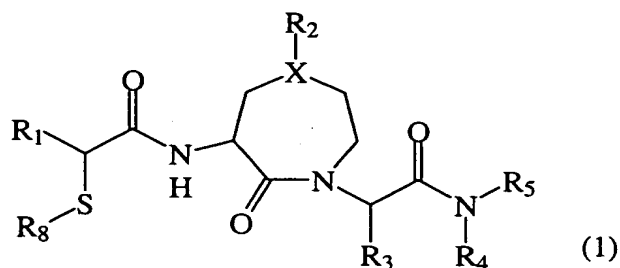


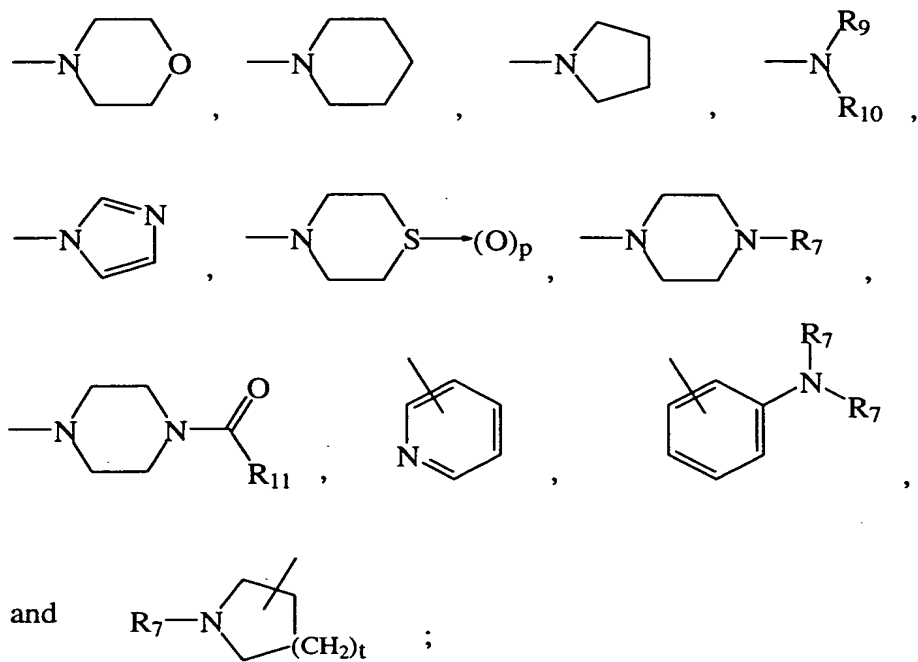
WHAT IS CLAIMED IS:

1. A compound of the formula

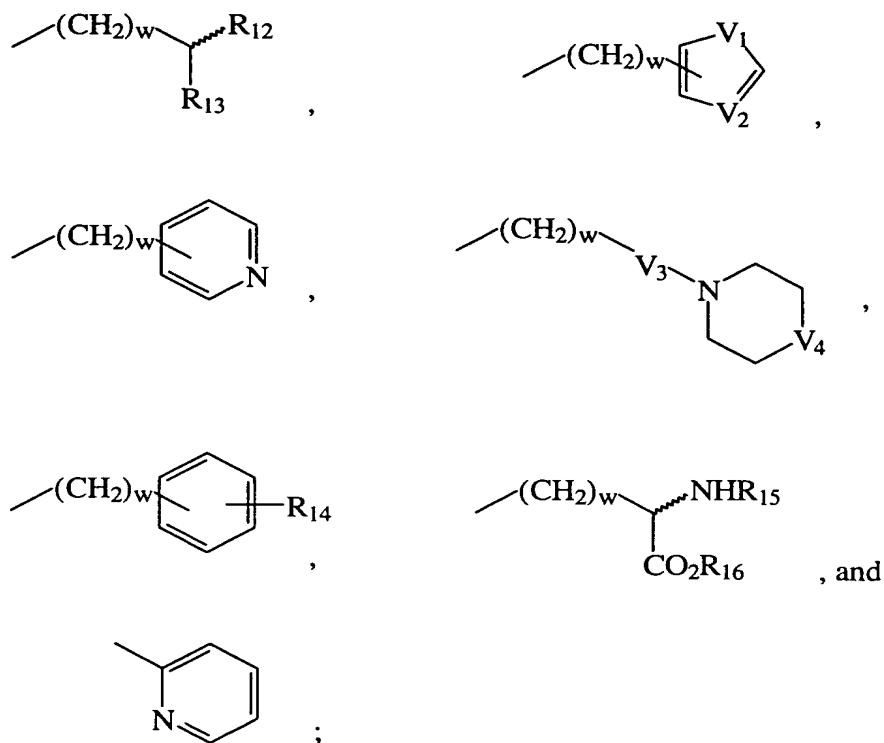


wherein

- R<sub>1</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, a W-(CH<sub>2</sub>)<sub>m</sub>- group, or a Q-Z-(CH<sub>2</sub>)<sub>m</sub>- group wherein W is phthalimido; Z is a bond or is oxy, NR<sub>6</sub>, C(O)NR<sub>6</sub>, NR<sub>6</sub>C(O), NHC(O)NR<sub>6</sub>, OC(O)NR<sub>6</sub>, HNC(O)O, or SO<sub>2</sub>NR<sub>6</sub>; Q is hydrogen, or a Y-(CH<sub>2</sub>)<sub>n</sub>- group wherein Y is hydrogen, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>9</sub> heteroaryl, -C(O)OR<sub>6</sub>, -N(R<sub>6</sub>)<sub>2</sub>, morpholino, piperidino, pyrrolidino, or isoindolyl;
- R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, a -(CH<sub>2</sub>)<sub>p</sub>-(C<sub>3</sub>-C<sub>9</sub>)heteroaryl group, or a -(CH<sub>2</sub>)<sub>p</sub>-Ar<sub>1</sub> group wherein Ar<sub>1</sub> is phenyl or naphthyl optionally substituted with a substituent selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, -OR<sub>7</sub>, -N(R<sub>6</sub>)<sub>2</sub>, SO<sub>2</sub>N(R<sub>6</sub>)<sub>2</sub> or -NO<sub>2</sub>;
- R<sub>3</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH<sub>2</sub>SCH<sub>2</sub>NHCOCH<sub>3</sub>, a -(CH<sub>2</sub>)<sub>p</sub>-A group, a -(CH<sub>2</sub>)<sub>m</sub>-B group or a -CH<sub>2</sub>-D-R<sub>7</sub> group wherein A is C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>9</sub> heteroaryl, or cyclohexyl; B is -N(R<sub>7</sub>)<sub>2</sub>, guanidino, nitroguanidino, -C(O)OR<sub>6</sub> or -C(O)NR<sub>6</sub>; and D is oxy or thio;
- R<sub>4</sub> is hydrogen or a -(CH<sub>2</sub>)<sub>m</sub>-S(O)<sub>p</sub>X'(R<sub>6</sub>)<sub>2</sub> group;
- R<sub>5</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or R<sub>4</sub> and R<sub>5</sub> taken together with the nitrogen atom to which they are attached form piperidino, pyrrolidino, or isoindolyl;
- R<sub>6</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sub>7</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or a -(CH<sub>2</sub>)<sub>p</sub>-Ar<sub>2</sub> group wherein Ar<sub>2</sub> is phenyl or naphthyl optionally substituted with a substituent selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, -OR<sub>7</sub>, -N(R<sub>6</sub>)<sub>2</sub>, SO<sub>2</sub>N(R<sub>6</sub>)<sub>2</sub> or -NO<sub>2</sub>;
- R<sub>8</sub> is hydrogen, -C(O)R<sub>7</sub>, a -C(O)-(CH<sub>2</sub>)<sub>q</sub>-K group or a -S-G group, wherein K is selected from the group consisting of



G is selected from the group consisting of



- 5  $\text{R}_9$  and  $\text{R}_{10}$  are each independently  $\text{C}_1\text{--C}_4$  alkyl or a  $\text{---}(\text{CH}_2)_p\text{---Ar}_2$  group;  
 $\text{R}_{11}$  is  $\text{---CF}_3$ ,  $\text{C}_1\text{--C}_{10}$  alkyl or a  $\text{---}(\text{CH}_2)_p\text{---Ar}_2$  group;

R<sub>12</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH<sub>2</sub>CH<sub>2</sub>S(O)<sub>p</sub>CH<sub>3</sub>, or arylalkyl;

R<sub>13</sub> is hydrogen, hydroxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl, N-methylamino, N,N-dimethylamino, -CO<sub>2</sub>R<sub>17</sub> or -OC(O)R<sub>18</sub> wherein R<sub>17</sub> is hydrogen, -CH<sub>2</sub>O-C(O)C(CH<sub>3</sub>)<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, a -(CH<sub>2</sub>)<sub>p</sub>-Ar<sub>2</sub> group or diphenylmethyl and R<sub>18</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl;

5 R<sub>14</sub> is 1 or 2 substituents independently chosen from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen;

R<sub>15</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or a -(CH<sub>2</sub>)<sub>p</sub>-Ar<sub>2</sub> group;

R<sub>16</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

V<sub>1</sub> is O, S, or NH;

10 V<sub>2</sub> is N or CH;

V<sub>3</sub> is a bond or -C(O)-;

V<sub>4</sub> is -(CH<sub>2</sub>)<sub>w</sub>-, O, S, NR<sub>7</sub>, or NC(O)R<sub>11</sub>;

X and X' are each independently CH or N;

m is an integer 2-4;

15 n is zero or an integer 1-4;

p is zero or an integer 1-2;

q is zero or an integer 1-5;

t is an integer 1-2;

w is an integer 1-3; and

20 w' is zero or an integer 1; or

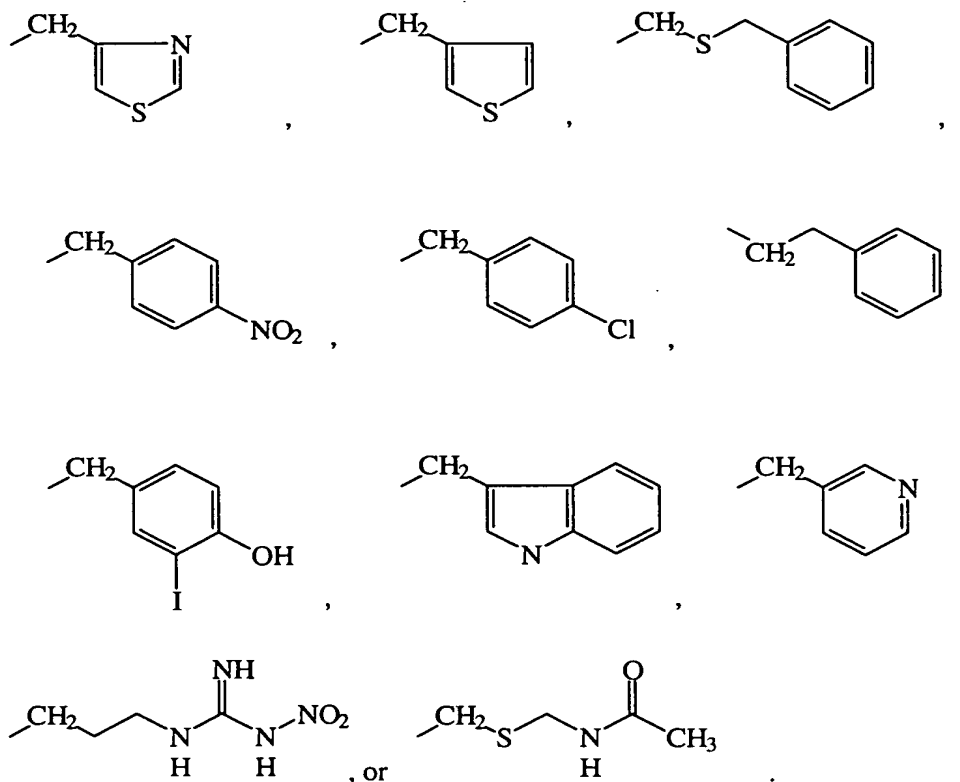
a pharmaceutically acceptable salt, stereoisomer or hydrate thereof.

2. A compound of claim 1 wherein X is CH.

25 3. A compound of claim 2 wherein R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or a -(CH<sub>2</sub>)<sub>p</sub>-Ar group wherein Ar is phenyl optionally substituted with F, Cl, C<sub>1</sub>-C<sub>4</sub> alkyl, -NO<sub>2</sub>, -NH<sub>2</sub> or -OR<sub>7</sub>; and R<sub>4</sub> is hydrogen.

30 4. A compound of claim 3 wherein R<sub>3</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, benzyl, 1-naphthyl, 2-naphthyl, cyclohexylmethyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-bromophenyl, 3,4-dibromophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3-tolyl, 4-tolyl, 4-

ethylphenyl, 4-isopropylphenyl, 3-aminophenyl, 4-aminophenyl, 3,4-diaminophenyl, N-methyl-4-aminophenyl, 2-nitrophenyl, 4-nitrophenyl, 4-aminobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 3,4-dichlorobenzyl, 4-bromobenzyl, 4-methylbenzyl,  $-\text{CH}_2\text{SCH}_2\text{NHCOCH}_3$ , or is a compound of the formula



5. A compound of claim 4 wherein  $R_5$  is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or isobutyl and  $R_8$  is hydrogen.

6. A compound of claim 2 wherein  $R_1$  is a  $W-(\text{CH}_2)_m$ - group.

7. A compound of claim 3 wherein  $R_1$  is a  $W-(\text{CH}_2)_m$ - group.

8. A compound of claim 5 wherein  $R_1$  is a  $W-(\text{CH}_2)_m$ - group.

9. A compound of claim 2 wherein  $R_1$  is  $C_1$ - $C_6$  alkyl.

10. A compound of claim 3 wherein  $R_1$  is  $C_1$ - $C_6$  alkyl.

11. A compound of claim 5 wherein  $R_1$  is a  $C_1$ - $C_6$  alkyl.

12. A compound of claim 2 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$ - group.

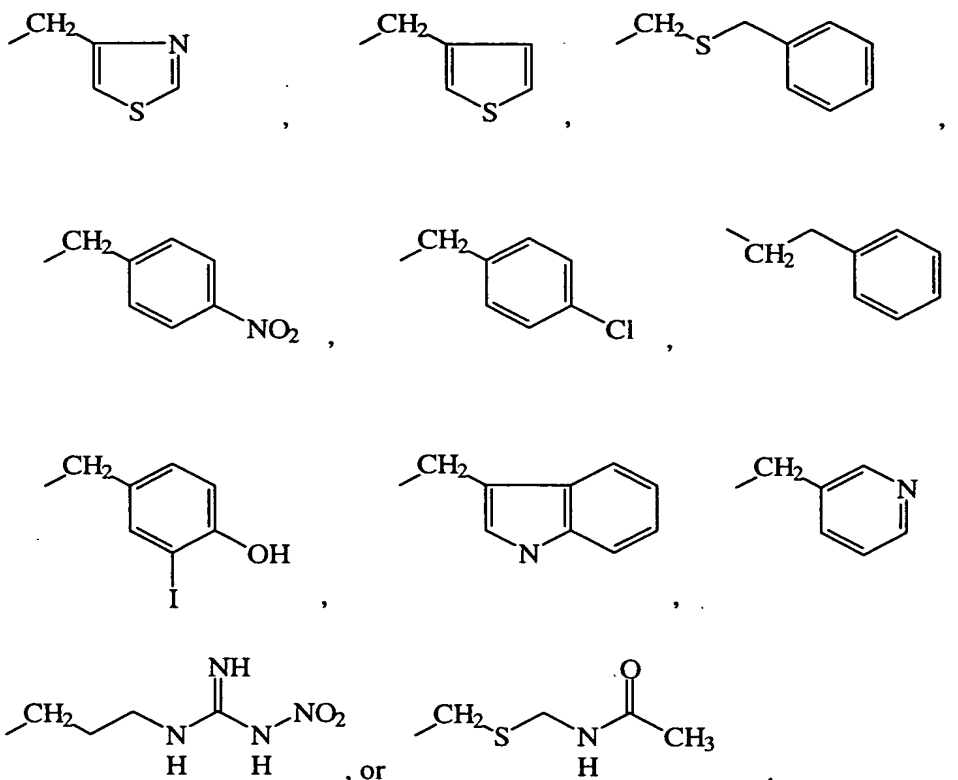
13. A compound of claim 3 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$ - group.

14. A compound of claim 5 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$ - group.

15. A compound of claim 1 wherein X is N.

16. A compound of claim 15 wherein  $R_2$  is  $C_1$ - $C_4$  alkyl or a  $-(CH_2)_p$ -Ar group wherein Ar is phenyl optionally substituted with F, Cl,  $C_1$ - $C_4$  alkyl,  $-NO_2$ ,  $-NH_2$  or  $-OR_8$ ; and  $R_4$  is hydrogen.

17. A compound of claim 16 wherein  $R_3$  is hydrogen,  $C_1$ - $C_6$  alkyl, phenyl, benzyl, 1-naphthyl, 2-naphthyl, cyclohexylmethyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-bromophenyl, 3,4-dibromophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3-tolyl, 4-tolyl, 4-ethylphenyl, 4-isopropylphenyl, 3-aminophenyl, 4-aminophenyl, 3,4-diaminophenyl, N-methyl-4-aminophenyl, 2-nitrophenyl, 4-nitrophenyl, 4-aminobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 3,4-dichlorobenzyl, 4-bromobenzyl, 4-methylbenzyl,  $-CH_2SCH_2NHCOCH_3$ , or is a compound of the formula



18. A compound of claim 17 wherein  $R_5$  is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or isobutyl and  $R_8$  is hydrogen.

19. A compound of claim 16 wherein  $R_1$  is a  $W-(CH_2)_m$  group.

20. A compound of claim 17 wherein  $R_1$  is a  $W-(CH_2)_m$  group.

21. A compound of claim 19 wherein  $R_1$  is a  $W-(CH_2)_m$  group.

22. A compound of claim 16 wherein  $R_1$  is  $C_1-C_6$  alkyl.

23. A compound of claim 17 wherein  $R_1$  is  $C_1-C_6$  alkyl.

24. A compound of claim 19 wherein  $R_1$  is a  $C_1-C_6$  alkyl.

25. A compound of claim 16 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$  group.

26. A compound of claim 17 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$ - group.

27. A compound of claim 19 wherein  $R_1$  is a  $Q-Z-(CH_2)_m$ - group.

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28. A compound of claim 1 wherein  $X$  is  $CH$ ;  $R_2$  is phenyl, methyl or ethyl;  $R_3$  is phenyl, benzyl, cyclohexylmethyl, isopropyl, isobutyl, 3-pyridylmethyl, 4-fluorobenzyl or 4-aminobenzyl;  $R_4$  is hydrogen;  $R_5$  is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or isobutyl and  $R_8$  is hydrogen.

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29. A compound of claim 28 wherein  $R_1$  is a  $W-(CH_2)_m$ - group.

30. A compound of claim 1 wherein  $X$  is  $N$ ;  $R_2$  is phenyl, methyl or ethyl;  $R_3$  is phenyl, benzyl, cyclohexylmethyl, isopropyl, isobutyl, 3-pyridylmethyl, 4-fluorobenzyl or 4-aminobenzyl;  $R_4$  is hydrogen;  $R_5$  is hydrogen, methyl, ethyl, , propyl, isopropyl, butyl or isobutyl and  $R_8$  is hydrogen.

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31. A compound of claim 30 wherein  $R_1$  is a  $W-(CH_2)_m$ - group.

32. A compound of claim 1 wherein said compound is 2*H*-Isoindole-2-hexanamide, *N*-[hexahydro-1-[2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl]-2-oxo-5-phenyl-1*H*-azepin-3-yl]-1,3-dihydro- $\alpha$ -mercapto-1,3-dioxo-, [3*S*-[1(*R*\*), 3 $\alpha$ , 5 $\alpha$ ]]-.

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33. A compound of claim 1 wherein said compound is 2*H*-Isoindole-2-hexanamide, *N*-[hexahydro-1-[2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl]-2-oxo-5-phenyl-1*H*-azepin-3-yl]-1,3-dihydro- $\alpha$ -mercapto-1,3-dioxo-, [3*S*-[1(*R*\*), 3 $\alpha$ , 5 $\beta$ ]]-.

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34. A compound of claim 1 wherein said compound is 2*H*-Isoindole-2-hexanamide, *N*-[hexahydro-4-[2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl]-5-oxo-1-(phenylmethyl)-1*H*-1,4-diazepin-6-yl]-1,3-dihydro- $\alpha$ -mercapto-1,3-dioxo-, [6*S*-[4(*R*\*), 6*R*\*(*R*\*)]]-.

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35. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

36. A method of inhibiting matrix metalloproteinase in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

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37. A method of inhibiting MMP-induced tissue disruption and/or MMP-induced tissue degradation in a patient in need thereof which comprises administering to the patient and effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

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38. A method of treating rheumatoid arthritis in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

39. A method of treating osteoarthritis in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

40. A method of treating a chronic inflammatory disorder in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

41. A method of treating a neoplastic disease state in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

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42. A method of treating a cardiovascular disorder in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

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43. A method of claim 42 wherein said cardiovascular disorder is atherosclerosis.



44. A method of treating corneal ulceration in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

5           45. A method of treating gingivitis or periodontal disease in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

10           46. A method of treating multiple sclerosis in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

15           47. A method of treating chronic obstructive pulmonary disorder in a patient in need thereof which comprises administering to the patient an effective matrix metalloproteinase inhibiting amount of a compound of claim 1.

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